PROHEXADIONE CALCIUM

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1/5/99

DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity Study in Rabbits with Range-finding Study
OPPTS Number: 870.3700 OPP Guideline Number: §83-3b

DP BARCODE: D246707 SUBMISSION CODE: S543930
P.C. CODE: 112600 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Prohexadione calcium (89.8-93.2% a.i.)

SYNONYMS: Cyclohexanecarboxylic acid; calcium salt of 3,5-dioxo-4-propionyl-cyclohexane-1-carboxylic acid; BX-112

CITATION(s): York, R.G. (1990) Teratology Study in Rabbits with BX-112. International Research and Development Corporation, Mattawan, MI, Laboratory Project ID. 442-029, March 30, 1990. MRID 44457760. Unpublished.

Schardein, J.L. (1989) Range-finding Teratology Study in Rabbits with BX-112. International Research and Development Corporation, Mattawan, MI, Laboratory Project ID. 442-028, May 18, 1989. MRID 44457759. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, North Carolina

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44457760 and 44457759), prohexadione calcium (89.8-93.2% a.i.) was administered by gavage at 0, 40, 200, or 750 mg/kg/day to pregnant New Zealand White SPF rabbits (20 females/dose) on gestation days (GDs) 7-19. Does were sacrificed on GD 29. One control doe aborted on GD 27 and was subsequently sacrificed; all other control animals survived to scheduled sacrifice. At 40 mg/kg, one doe was sacrificed *in extremis* on GD 25.

Due to severe mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of maternal toxicity. At 200 mg/kg, four deaths (one following an abortion) occurred during GDs 15-24. At 200 mg/kg, body weight gains were reduced prior to treatment (↓54%, GDs 0-7), during the treatment interval, (↓203%, GDs 7-13, $p<0.05$), for the overall treatment interval (↓1044%, GDs 7-20, $p<0.05$), and for the overall study interval (↓1686%, GDs 0-29). At 200 mg/kg five abortions were also observed from GDs 24-29. Total number of corpora lutea (↓50%)

and implantations (↓48%) were reduced (p=not statistically significant); in turn, a reduced (p=not statistically significant) number of does with viable fetuses (↓47%) and total number of live fetuses (↓45%) were observed. At 750 mg/kg, 15 deaths occurred during GDs 9-16, one premature delivery occurred on GD 26, and one doe was sacrificed *in extremis* on GD 26. Body weight gains were decreased during the treatment interval (GDs 7-13, $p<0.01$), during post-treatment, (GDs 20-24, $p<0.01$), and for the overall treatment interval, (GDs 7-20). Gross pathological findings at 750 mg/kg included 8/20 animals with lung congestion vs 1/20 controls and 7/20 animals with stomach erosion/ulcerations vs 0/20 controls. **The maternal NOAEL is 40 mg/kg/day. The maternal LOAEL is 200 mg/kg/day, based on increased mortality and abortions and decreased body weight gains.**

Due to the severe mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of developmental parameters. There were no treatment-related developmental effects noted at any dose level. **The developmental NOAEL is ≥200 mg/kg/day. The developmental LOAEL was not observed.**

This developmental toxicity study is classified **acceptable (§83-3[b])** and does satisfy the guideline requirement for a developmental toxicity study in the rabbit; however, this study should not be used for regulatory purposes due to the increased mortality. (See Comments below.)

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

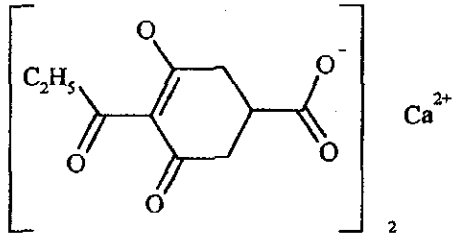
COMMENTS:

1. The HIARC concluded that this study should not be used to establish endpoints for risk assessment because the deaths seen at 200 mg/kg/day could be a lab-related problem and deaths were not seen at similar doses (100, 150, or 350 mg/kg/day) in two other rabbit developmental studies (MRID 44457762 and 44457761).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Prohexadione calcium
   Description: Tan powder
   Lot/Batch #: G14-04, G14-06
   Purity: 89.8-93.2% a.i.
   Storage: Refrigeration
   CAS #: 127277-53-6
   Structure:



2. Vehicle: 0.5% carboxymethylcellulose

3. Test animals: Species: Rabbit
   Strain: New Zealand White SPF
   Age and weight of females at mating: 7 months old, 4021-5240 g
   Source: Hazleton Research Products, Denver, PA
   Housing: Individually in suspended stainless steel cages
   Diet: Certified Rabbit Chow® #5322, at receipt, fed 60 g/day, increased in 30 g increments until fed ad libitum approximately 2 weeks after receipt
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 70-74°F
   Humidity: 51-55%
   Air changes: Not reported
   Photoperiod: 12 hrs dark/12 hrs light
   Acclimation period: 90 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 5/10/89 end: 6/10/89

2. Mating: Approximately 3 weeks prior to insemination, females received an injection of human chorionic gonadotropin (HCG). Semen was collected from stock rabbits of the same source and strain. Females were artificially inseminated and ovulation was induced by an injection of HCG. Insemination was conducted over a 3 day period and the day of insemination was designated as gestation day (GD) 0.

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3. Animal assignment: Animals were randomly assigned to dose groups by a computer-generated system (stratified by weight) as indicated in Table 1.

Table 1. Animal assignment

Test Group	Dose (mg/kg/day)	Concentration (mg/mL)	Number of Females
Control	0	0	20
Low	40	13.33	20
Mid	200	66.67	20
High	750	250	20

4. Dose selection rationale: In a range-finding study reviewed with the current submission (MRID 44457759), prohexadione calcium (89.8% a.i.) in a 0.5% aqueous solution of carboxymethylcellulose was administered orally via gavage to 6 inseminated female New Zealand White SPF rabbits/dose at dosages of 0, 100, 250, 500, or 1000 mg/kg/day on GDs 7 through 19. Animals were sacrificed on GD 29. No statistical analysis information was provided.

Maternal toxicity was characterized by death or sacrifice *in extremis* of two 500 mg/kg does and three 1000 mg/kg does. Upon necropsy, lung congestion was noted in one 500 mg/kg doe and in two 1000 mg/kg does; also noted in the 1000 mg/kg does was gastric irritation including discoloration and hemorrhaging. Two abortions occurred, one each at the 500 and 1000 mg/kg levels. Inflammatory liver and lung foci and stomach erosions were observed in one 1000 mg/kg doe at necropsy. Anogenital staining was observed in all 1000 mg/kg does that died or were sacrificed during the study, in one 500 mg/kg doe that survived to scheduled sacrifice, and in one 250 mg/kg doe.

Body weights of treated animals were comparable to or higher than controls throughout the study. Treatment-related reductions in body weight gains were observed in all treated groups on GDs 7-13 (100 mg/kg, ↓57%; 250 mg/kg, ↓117%; 500 mg/kg, ↓169%; 1000 mg/kg, ↓245%). On GDs 13-20, body weight gains rebounded at 100 mg/kg (↑334%) and 250 mg/kg (↑200%), but were reduced at 500 mg/kg (↓128%) and 1000 mg/kg (↓286%). Following treatment (GDs 20-29), body weight gains were reduced in the 100 mg/kg does (↓139-16,600%). For the overall treatment interval (GDs 7-19), body weight gains increased at 100 mg/kg (↑11%), but decreased at the 250 mg/kg (↓61%), 500 mg/kg (↓93%), and 1000 mg/kg (↓171%) levels. Weight gains for the overall study interval (GDs 0-29) were lower at the 100 mg/kg (↓57%), 250 mg/kg (↓10%), and 1000 mg/kg (↓28%) levels and increased at 500 mg/kg (↑21%).

At 1000 mg/kg, treatment-related increases in postimplantation loss/doe (↑733%), group

mean preimplantation loss (↑23%), and group mean postimplantation loss (↑800%) indices were noted; in addition, the number of viable fetuses/doe was reduced (↓43%).

No fetal observation data were submitted. The study report stated that one 100 mg/kg fetus exhibited several malformations, including encephalocele, microcephaly, cleft palate, ablepharia, microphthalmia, short upper jaw, microtia, open auditory canal, forelimb ectrodactyly, adactyly, and gastroschisis; however, these findings were limited to the single fetus and considered not to be treatment-related.

Based on the results of this range finding study, the doses presented in Table 1 were selected for the subsequent full developmental toxicity study.

5. Dosage preparation and analysis - Dose solutions were prepared weekly by mixing the appropriate amount of test substance with 0.5% carboxymethylcellulose; solutions were stored under refrigeration. Prior to the study, dose formulations of 13.33, 66.67, and 250 mg/mL were evaluated for homogeneity (top, middle, bottom) and stability. For stability analyses, samples were stored under refrigeration for 24 hours to simulate dosing conditions; in addition, samples were also stored under refrigeration for up to 10 days. During the study, concentration analyses were performed twice on the dose formulations. All samples were examined in duplicate.

   Results - Homogeneity analysis (% of nominal±S.D.): low-dose, 89±1.9%; mid-dose, 100±1.6%; high-dose, 102±0.9%.

   Stability analysis: Samples stored for 24 hours were 101-104% of nominal. Samples stored for 10 days were 99-101% of nominal.

   Concentration analysis (mean % of nominal): 13.33 mg/mL formulation, 91%; 66.67 mg/mL formulation, 104%; 250 mg/mL formulation, 104%.

   The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. Dosage administration: All doses were administered once daily by gavage on GDs 7 through 19 in a volume of 3 mL/kg body weight. Dosing was based on GD 7 body weights. Control animals received the vehicle only.

C. OBSERVATIONS

1. Maternal observations and evaluations - The animals were checked for mortality and clinical signs of toxicity twice daily. Body weight data were recorded on GDs 0, 7, 13, 20, 24, and 29. Food consumption was not measured. Does were sacrificed on GD 29. Examinations at sacrifice consisted of a gross exam of the thoracic and abdominal cavities. The reproductive tract was removed, examined, and the following were recorded:

- number of corpora lutea in each ovary
- number of implantation sites
- number and distribution of fetuses (live and dead)
- number and distribution of resorptions (early and late)

The uteri of non-pregnant females were opened and placed in 10% ammonium sulfide for detection of implantations.

2. Fetal evaluations - All fetuses were weighed, sexed, examined for external abnormalities, and subjected to a visceral examination including an examination of the brain by a mid-coronal slice and the heart according to a modified STAPLE'S technique. All fetuses were eviscerated, skinned, fixed in alcohol, macerated (KOH), stained with alizarin red S, and cleared according to a modified DAWSON's technique to allow for skeletal examination. Fetuses from does that died, aborted, delivered, or were sacrificed near term were necropsied and examined.

D. DATA ANALYSIS

1. Statistical analyses: All data collected were subjected to routine appropriate statistical procedures.

2. Indices: The following indices were calculated by the investigator:

   Group mean preimplantation loss:
   # corpora lutea - # implantations/# corpora lutea x 100

   Group mean postimplantation loss:
   # implantations - # viable fetuses/# implantations x 100

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical observations: One control doe aborted on GD 27 and was subsequently sacrificed; all other control animals survived to scheduled sacrifice. At 40 mg/kg, one doe was sacrificed *in extremis* on GD 25. It was stated that this 40 mg/kg doe had loss of the righting reflex and splayed limbs that may have resulted from a back injury; no cause of injury was determined. From GDs 15-24, four deaths (one following an abortion) occurred at 200 mg/kg. At 750 mg/kg, 15 deaths occurred during GDs 9-16 and one doe was sacrificed *in extremis* on GD 26.

2. Body weight: When compared to concurrent controls, no treatment-related differences in

mean body weights were observed. Body weight gain reductions (Table 2) were noted in all treated animals including controls. Due to the increased mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of body weight parameters. During pretreatment (GDs 0-7), body weight gains were reduced at 200 mg/kg (↓54%). During the treatment interval decreases ($p<0.05$) in body weight gains were noted at 200 mg/kg (↓203 %) and 750 mg/kg ; body weight gains were also reduced at 40 mg/kg (p=not statistically significant) when compared to concurrent controls. During post-treatment (GDs 20-24), body weight gains decreased at 750 mg/kg ($p<0.01$). For the overall treatment interval (GDs 7-20), body weight gains were reduced at 200 mg/kg ($p<0.05$) and 750 mg/kg (↓894%); for the overall study interval (GDs 0-29) body weight gains decreased at 200 mg/kg.

Fifteen high-dose does died during the treatment interval and one high-dose female was non-gravid and excluded from the body weight gain calculation leaving only 4 does to evaluate on GD 20; following one premature delivery and one sacrifice *in extremis*, only 2 high-dose does remained at GD 29.

Table 2. Mean (±SE) maternal body weight gains (g) [a]

Interval	Dose in mg/kg/day 0	40	200	750
Pretreatment:				
Days 0-7	118±82.6 (18)	110±125.4 (19)	54±186.2 (17)	122±59.8 (17)
Treatment:				
Days 7-13	39±57.0 (18)	53±97.0 (19)	-40±108.4 (17) *	-352±242.1 (10) **
Days 13-20	-21±184.4 (18)	-36±196.7 (19)	-151±216.0 (16)	-49±393.7 (4)
Post treatment:				
Days 20-24	-47±97.4 (18)	-11±120.6 (19)	-41±98.5 (13)	-248±152.3 (4) **
Days 24-29	-106±133.1 (17)	-75±166.6 (18)	-73±146.1 (10)	150±181.7 (2)
Overall treatment:				
Days 7-20	18±182.9 (18)	17±235.9 (19)	-170±229.6 (16) *	-143±283.3 (4)
Overall:				
Days 0-29	7±300.3 (17)	77±281.4 (18)	-111±378.2 (10)	170±144.2 (2)

a Data extracted from the study report, Table 2, page 30.
b Number of does presented parenthetically.
* or ** Significantly different from controls at $p<0.05$ or 0.01.

3. Food consumption - Food consumption data were not submitted and are not required based on Subdivision F Guidelines because this study is not a dose-feeding study.

4. Gross pathology - No treatment-related gross pathological findings were noted at the low- or mid-dose levels. Findings observed at 750 mg/kg considered to be related to treatment

included 8/20 animals with lung congestion vs 1/20 controls and 7/20 animals with stomach erosion/ulcerations vs 0/20 controls.

5. Cesarean section data - Cesarean section observations are presented in Table 3. Does that died, aborted, or were sacrificed *in extremis* were excluded from Cesarean section parameters; however, two aborted 200 mg/kg litters and two dead control fetuses were included in the examination for developmental abnormalities.

   One control doe aborted on GD 27 and was subsequently sacrificed *in extremis*. From GDs 15-24, four deaths occurred at the 200 mg/kg level. At 750 mg/kg, 15 deaths occurred during GDs 9-16 and one doe was sacrificed *in extremis* on GD 26. Due to the increased mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of Cesarean section parameters. At 200 mg/kg, five abortions (death following in one case on GD 24) occurred during GDs 24-29. At 750 mg/kg, one premature delivery occurred on GD 26. At 200 mg/kg, reduced (p=not statistically significant) total number of corpora lutea (↓50%) and implantations (↓48%) were observed; in turn, the number of does with viable fetuses (↓47%) and total number of live fetuses (↓45%) were reduced (p=not statistically significant). No differences in number of resorptions, mean fetal weights, percent male, or pre- and postimplantation losses were observed at any dose level.

Table 3. Cesarean section observations [a]

Observation	Dose (mg/kg/day)			
	0	40	200	750
# Animals Mated	20	20	20	20
# Animals Pregnant	18	19	17	17
Pregnancy Rate (%)	(90)	(95)	(85)	(85)
# Nonpregnant	2	1	3	3
# Total Does Died	0	0	3 [c]	15
# Died Pregnant	0	0	3 [c]	13
# Died Nonpregnant	0	0	0	2
# Does Sacrificed *in extremis*	0	1	0	1
# Does Sacrificed *in extremis* Pregnant	0	1	0	1
# Does Sacrificed *in extremis* Nonpregnant	0	0	0	0
# Aborted	1	0	5 [c]	0
# Premature Delivery	0	0	0	1
Total # Corpora Lutea [b]	281	284	140	37
Corpora Lutea/Doe	16.5±5.81	15.8±4.01	15.6±4.90	18.5±4.95
Total # Implantations [b]	143	137	75	18
Implantations/Doe	8.4±3.86	7.6±3.01	8.3±2.0	9.0±1.41
Does with Viable Fetuses	17	18	9	2
Total # Live Fetuses	127	122	70	15
Live Fetuses/Doe	7.5±3.74	6.8±2.76	7.8±2.17	7.5±0.71
Total # Dead Fetuses [b]	2	1	0	0
Dead Fetuses/Doe	NR	NR	0	0
Total # Litters Examined	17	18	11 [d]	2
Total # Fetuses Examined	129 [e]	122	88	15
Total # Resorptions [b]	14	14	5	3
Early	6	10	5	0
Late	8	4	0	3
Resorptions/Doe	NR	NR	NR	NR
Early	NR	NR	NR	NR
Late	NR	NR	NR	NR
Litters with Total Resorptions	0	0	0	0
Mean Fetal Weight (g)	41.2±9.54	44.4±9.08	41.5±5.63	41.3±1.84
Males	NR	NR	NR	NR
Females	NR	NR	NR	NR
Sex Ratio (% Male)	42.6	54.1	47.1	46.7
Preimplantation Loss (%)	49.1	51.8	46.4	51.4
Postimplantation Loss (%)	11.2	10.9	6.7	16.7

a Data extracted from the study report, Tables 3 and 4, pages 31 and 32 and pages 54 through 57; NR=Not reported.
b Calculated by reviewers.
c One doe died following an abortion and was not included in the total # of does died or died while pregnant.
d Two aborted litters were examined for developmental parameters.
e Two dead fetuses were examined for developmental parameters.

B. DEVELOPMENTAL TOXICITY: Fetal examinations included external, visceral, and skeletal observations at necropsy.

1. External examination - There were no treatment-related external malformations or variations detected at any dose level. The only external observation is shown in Table 4a.

Table 4a. External examinations [a, b]

Observations	Dose (mg/kg/day)			
	0	40	200	750
#Fetuses (#litters) examined	129 (17)	122 (18)	88 (11)	15 (2)
Malformations				
Hydrocephaly	0.8 (5.9)	0 (0)	0 (0)	0 (0)

a Data extracted from the study report, Table 4, page 32.
b For individual observations, data are presented as % fetal incidence (% litter incidence). Both were calculated by reviewers.

2. Visceral examination - There were no treatment-related visceral malformations or variations observed at any dose level. The most common findings are presented in Table 4b. Left carotid stenosis was noted in one high-dose fetus and was considered to be an incidental finding.

Table 4b. Visceral examinations [a, b]

Observations	Dose (mg/kg/day)			
	0	40	200	750
#Fetuses (#litters) examined	129 (17)	122 (18)	88 (11)	15 (2)
Malformations				
Left carotid stenosis	0 (0)	0 (0)	0 (0)	6.7 (50.0)
Gallbladder agenesis	0 (0)	2.5 (5.6)	0 (0)	0 (0)

a Data extracted from the study report, Table 4, page 32.
b For individual observations, data are presented as % fetal incidence (% litter incidence). Both were calculated by reviewers.

3. Skeletal examination - There were no treatment-related skeletal malformations or variations observed at any dose level. The most common skeletal findings are presented in Table 4c.

Table 4c. Skeletal examinations [a, b]

Observation	Dose (mg/kg/day)			
	0	40	200	750
#Fetuses (#litters) examined	129 (17)	122 (18)	88 (11)	15 (2)
Malformations				
Interrupted ossification of an arch	0 (0)	0.8 (5.6)	0 (0)	0 (0)
Vertebral malformation with an associated rib malformation	0.8 (5.9)	0 (0)	0 (0)	0 (0)
Interrupted ossification of a rib	0 (0)	0 (0)	1.1 (9.1)	0 (0)
Sternoschisis	0.8 (5.9)	0 (0)	0 (0)	0 (0)
Fused sternebra	0.8 (5.9)	0 (0)	0 (0)	0 (0)
Forked scapula	0.8 (5.9)	0 (0)	0 (0)	0 (0)

a Data extracted from the study report, Table 4, page 32.
b For individual observations, data are presented as % fetal incidence (% litter incidence). Both were calculated by reviewers.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS - Administration of prohexadione calcium resulted in maternal toxicity characterized by four deaths at the 200 mg/kg and 15 deaths at the 750 mg/kg levels. Stomach erosions at 750 mg/kg and 5 abortions at 200 mg/kg were related to treatment. Observations thought to be indirectly related to treatment were decreased defecation at the 200 and 750 mg/kg levels and lung congestion at 750 mg/kg. Reduced body weight gains at 200 and 750 mg/kg were noted for the overall treatment interval (GDs 7-20). The maternal LOAEL is 200 mg/kg and the NOAEL is 40 mg/kg/day.

There were no treatment-related external, visceral, or skeletal malformations or variations in this study. No observed developmental toxicity existed at 750 mg/kg, however, data for this dose were limited to 2 animals. The developmental LOAEL is 750 mg/kg/day and the NOAEL is 200 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Prohexadione calcium (89.8-93.2% a.i.) was administered by gavage at 0, 40, 200, or 750 mg/kg/day to pregnant New Zealand White SPF rabbits (20 females/dose) on GDs 7-19. Does were sacrificed on GD 29. One control doe aborted on GD 27 and was subsequently sacrificed; all other control animals survived to scheduled

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sacrifice. At 40 mg/kg, one doe was sacrificed *in extremis* on GD 25. At 200 mg/kg, four deaths occurred from GDs 15-24 and five abortions (death following in one case) occurred during GDs 24-29. At 750 mg/kg, 15 deaths occurred during GDs 9-16, one premature delivery occurred on GD 26, and one doe was sacrificed *in extremis* on GD 26. No dose dependent, treatment-related clinical signs of toxicity were noted at any dose level.

Body weight gain reductions were noted in all treated animals including controls. Body weight gains were reduced at 40 mg/kg (p=not statistically significant) when compared to concurrent controls. Due to the increased mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of body weight parameters. At 200 mg/kg, body weight gains were reduced prior to treatment (↓54%, GDs 0-7), during the treatment interval, (↓203 %, GDs 7-13, $p<0.05$), for the overall treatment interval (↓1044%, GDs 7-20, $p<0.05$), and for the overall study interval (↓1686%, GDs 0-29).. At 750 mg/kg, body weight gains were decreased during the treatment interval (GDs 7-13, $p<0.01$), during post-treatment, (GDs 20-24, $p<0.01$), and for the overall treatment interval, (GDs 7-20).

Food consumption data were not submitted and are not required because this study is not a dose-feeding study.

Treatment-related gross pathological findings at 750 mg/kg included 8/20 animals with lung congestion vs 1/20 controls and 7/20 animals with stomach erosion/ulcerations vs 0/20 controls.

Due to the increased mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of Cesarean section parameters. At 200 mg/kg, total number of corpora lutea (↓50%) and implantations (↓48%) were reduced; in turn, number of does with viable fetuses (↓47%) and total number of live fetuses (↓45%) were reduced. No differences in number of resorptions, mean fetal weights, percent male, or pre- and postimplantation losses were observed.

The maternal LOAEL = 200 mg/kg/day, based on increased mortality and abortions and decreased body weight gains
The maternal NOAEL = 40 mg/kg/day

2. DEVELOPMENTAL TOXICITY: Due to the increased mortality at 750 mg/kg, 200 mg/kg was deemed the high-dose for evaluation of developmental parameters. There were no treatment-related developmental effects noted at any dose level.

   a. Deaths/Resorptions: The number of resorptions/dam and viable fetuses/dam for the treatment groups were not significantly different from the concurrent controls.
   b. Altered Growth: There were no treatment-related changes in fetal body weights at any dose level.
   c. Developmental Variations: There were no treatment-related developmental variations noted at any dose level.

d. Malformations: There were no treatment-related developmental malformations noted at any dose level.

The developmental NOAEL ≥200 mg/kg/day
The developmental LOAEL was not observed

This developmental toxicity study is classified acceptable (§83-3[b]) and does satisfy the guideline requirement for a developmental toxicity study in the rabbit; however, this study should not be used for regulatory purposes.

C. STUDY DEFICIENCIES - The following deficiencies were noted, but will not affect the conclusions of the report:

- Clinical signs and total number of corpora lutea, implantations, and resorptions were not reported in summary tables.

- In the rangefinding study, deaths occurred at 500 mg/kg/day; therefore, a high-dose of 750 mg/kg/day was too high and induced severe lethal toxicity.

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